Hemodynamic changes mimicking a vasodilator drug response in the absence of drug therapy after right heart catheterization in patients with chronic heart failure

Milton Packer, M.D., Norma Medina, R.N., and Madeleine Yushak, R.N.

ABSTRACT We suspected that patients with severe chronic heart failure may show hemodynamic changes after cardiac catheterization in the absence of drug therapy that could complicate assessment of the hemodynamic effects of new vasodilator and inotropic agents. To evaluate this phenomenon prospectively, hemodynamic variables were measured in 21 patients with heart failure 30 min and 2, 6, 24, and (in 12 patients) 48 hr after right heart catheterization, during which time therapy was not altered. During the first 2 hr we noted a significant increase in cardiac index and decreases in left ventricular filling pressure, mean arterial pressure, mean right atrial pressure, and systemic vascular resistance (p < .01); a further decline in left ventricular filling pressure was noted over the next 24 hr, after which all hemodynamic variables remained stable. The magnitude of these hemodynamic changes resembled the effects of many established vasodilator drugs and was further enhanced after meals. These data indicate that hemodynamic improvement may be observed without any therapeutic intervention during the course of invasive studies in patients with severe chronic heart failure; such changes may lead investigators to attribute efficacy to ineffective drug therapy. To minimize the occurrence of such responses, we recommend that intravascular catheters be inserted the day before drug evaluation and that hemodynamic measurements be made with patients in a postprandial state.


EVALUATION of the efficacy of cardiovascular drugs is complicated by the fact that patients may show beneficial responses during the course of therapy in the absence of effective treatment. Patients with coronary artery disease may experience a reduction in the frequency of anginal attacks while on placebo,1-4 patients with systemic hypertension may show small but sustained decreases in diastolic blood pressure while receiving no active drug,5-7 and patients with ventricular tachyarrhythmias may show spontaneous variation in the frequency and complexity of ectopic activity that may mimic a beneficial drug response even if no treatment has been administered.8-10 Such spontaneous therapeutic effects may result from the natural variability of the disease process8-12 or from bias introduced by the design of the clinical trial.2,5,13,14 Efforts to understand the source of such effects has aided in the design of studies that minimize spontaneous improvement and therefore can accurately assess the efficacy of promising new antianginal, antihypertensive, and antiarrhythmic drugs.2,5,14

In contrast to other cardiovascular disorders, there has been little appreciation that study design may influence therapeutic end points in the evaluation of drugs for severe chronic heart failure. Investigators have long assumed that such patients do not exhibit spontaneous hemodynamic or clinical changes that might mimic a therapeutic response; hence, any observed improvement has been attributed to drug therapy. However, recent trials in patients with heart failure have shown that patients with severe symptomatic left ventricular dysfunction can show marked increases in exercise duration while receiving placebo15; whether invasively derived hemodynamic variables may show similar degrees of spontaneous improvement in these patients is unknown.

In this article we report the occurrence of hemody-
namic changes that mimic a vasodilator drug response in patients with severe chronic heart failure after right heart catheterization and suggest guidelines for the design of future studies that should minimize the occurrence of these nonpharmacologic circulatory events.

Methods

Patients. We evaluated 21 patients with severe chronic heart failure who underwent invasive hemodynamic testing for treatment with vasodilator drugs. There were 16 men and five women, ranging in age from 27 to 75 years (mean 61). The cause of congestive heart failure was ischemic cardiomyopathy in 14 patients, primary dilated cardiomyopathy in six patients, and severe primary aortic valve regurgitation associated with severe left ventricular dysfunction in one patient; the left ventricular ejection fraction as determined by radionuclide ventriculography ranged from 11% to 21%. All patients had symptoms of dyspnea and/or fatigue on minimal exertion despite therapeutic doses of digoxin (0.125 to 0.25 mg daily) and furosemide (40 to 120 mg daily) but were clinically stable for at least 4 weeks at the time of evaluation; none had received treatment with vasodilator drugs for the previous 7 days.

Hemodynamic assessment. Before entry into the study, all patients were hospitalized for at least 5 days, during which time doses of digoxin and diuretics remained constant. All patients were fed a 2 g sodium diet and were transferred to the coronary care unit when body weight (measured before breakfast each morning) had not changed by more than 0.5 kg for at least 4 days. After an overnight rest and fast, the morning doses of digitalis and diuretics were withheld (so as not to interfere with the interpretation of subsequent hemodynamic measurements), and after written informed consent was obtained, right heart catheterization via an antecubital, subclavian, or internal jugular approach was performed under fluoroscopic guidance with a triple-lumen flow-directed catheter for measurement of right atrial, pulmonary arterial, and pulmonary capillary wedge pressures. Arterial cannulas were inserted into the radial artery of all patients for measurement of systemic pressures. All procedures were performed with local anesthesia and without premedication by the same physician (M. P.), and all hemodynamic measurements were made by one of two research nurse associates (N. M. or M. Y.) who had been specifically trained in performing reproducible hemodynamic determinations and had done so for the previous 5 years; neither had any other patient care responsibilities. All measurements in an individual patient throughout the trial were made by a single observer.

All hemodynamic determinations were made with zero reference level at the midaxillary line with the patient supine. To ensure reproducibility of this reference level for subsequent measurements and to avoid zero level drift, the transducer was anchored at the midaxillary line with the patient’s bed at maximum horizontal elevation, and before each measurement this juxtaposition was rechecked and evaluated with a carpenter’s level to avoid parallax artifacts. Before each hemodynamic determination, the identity of zero transducer pressure and atmospheric pressure was confirmed, and calibration scales were displayed electronically. Left ventricular filling pressure was measured as the mean pulmonary capillary wedge pressure. Thermodilution cardiac outputs were determined in triplicate by a bedside cardiac output computer with the use of iced injectate. Heart rates were derived from a continuously recorded electrocardiogram.

Thirty minutes after insertion of the intravascular catheters, the following hemodynamic variables were determined in triplicate over 30 ± 15 min with a variation of less than 10%: mean arterial pressure, heart rate, left ventricular filling pressure, mean right atrial pressure, and cardiac output. These variables were reassessed every 30 min for 2 hr, after which 14 of the 21 patients were permitted to eat lunch and were administered their daily doses of digoxin and diuretics. The remaining seven patients ingested their usual low-sodium meal, and hemodynamic variables were reassessed 1, 2, and 3 hr later to evaluate the circulatory effects of meal ingestion. Daily doses of digoxin and diuretics were not given to these patients until after these additional measurements were completed. The final hemodynamic determinations performed on this day were made just before dinner, 6 hr after completion of the invasive procedures.

The next morning (22 to 24 hr after right heart catheterization), after all medications and breakfast had been withheld, hemodynamic measurements were performed in triplicate in all 21 patients. Twelve of the 21 patients underwent a second day of drug-free hemodynamic determinations; their hemodynamic state was reassessed 1, 2, 3, 4, 6, and 8 hr after the initial morning measurements, during which time no drugs were given and no meals were eaten. This 8 hr period corresponded to the time of the day (0900 to 1700 hr) when postcatheterization and postprandial measurements had been made 24 hr earlier. At the end of this period, patients were fed and digoxin and diuretics were administered in their usual doses. The next morning after digoxin, diuretics, and breakfast had been again withheld, hemodynamic measurements were performed for a final time 46 to 48 hr after right heart catheterization.

During the entire period of the trial, patients did not receive any other cardioactive drugs and did not receive or require analgesic agents for pain. Except for the postprandial study in seven patients, all hemodynamic measurements were obtained after at least 14 hr in the postabsorptive state; patients were permitted only liquids during periods of hemodynamic assessment. Furthermore, they were kept at bed rest in a quiet room specifically designed for special studies, shielded from the remainder of the coronary care unit, and were permitted limited visitors for brief periods.

Data analysis. Mean systemic arterial pressures were determined by electronic filtration. Derived hemodynamic variables were calculated as follows:

\[
\text{cardiac index (CI)} = \frac{\text{CO} \times \text{body surface area (liters/min/m}^2\text{)}}\]

\[
\text{systemic vascular resistance (SVR)} = \frac{80 \times (\text{MAP} - \text{MRAP})}{\text{CO}} \times \text{dyne-sec-cm}^{-5}
\]

where CO = cardiac output, MAP = mean arterial pressure, and MRAP = mean right atrial pressure.

All hemodynamic data points for each patient at each point in time in this study represent the average of three separate hemodynamic determinations, each determination being the result of averaging at least five cardiac cycles. Hence, each data point represents approximately 15 separate measurements of right heart and systemic pressures, heart rate, and cardiac output. Hemodynamic changes during the course of the trial were compared with the control hemodynamic state by a repeated-measures analysis of variance procedure in which Duncan’s multiple range test was used to differentiate among significant responses. Group data were expressed as mean ± SEM.

Results

Postcatheterization hemodynamic changes. Significant hemodynamic changes were noted after completion of the first cardiac catheterization in the absence of vasodilator therapy. During the first 2 hr we observed small but sustained increases in cardiac index (+ 0.13 liter/min/m²) and decreases in left ventricular filling pres-
sure (−1.8 mm Hg), mean arterial pressure (−3.3 mm Hg), mean right atrial pressure (−2.0 mm Hg), and systemic vascular resistance (−269 dyne·sec·cm⁻²), all p < .01, without changes in heart rate (figure 1). Over the next 24 hr left ventricular filling pressure fell further (by 4.1 mm Hg, p < .01 vs 30 min and vs 2 hr), but without additional significant changes in cardiac index, mean arterial pressure, mean right atrial pressure, heart rate, or systemic vascular resistance.

The magnitude of these hemodynamic changes was highly variable. Over the course of 24 hr, cardiac index increased by greater than 0.50 liter/min/m² in six patients (as great as 0.71 liter/min/m²), left ventricular filling pressure fell more than 5 mm Hg in 11 patients (as much as 17 mm Hg), mean right atrial pressure decreased by more than 5 mm Hg in six patients (as great as 9 mm Hg), and systemic vascular resistance declined by more than 20% in seven patients (as much as 53%). No patient experienced a fall in cardiac index or rise in left ventricular filling pressure after catheterization.

Postprandial hemodynamic changes. In seven patients who consumed a low-sodium meal 2 hr after cardiac catheterization, we noted (1 hr later) further increases in cardiac index (1.77 ± 0.15 to 2.29 ± 0.15 liters/min/m²) and further decreases in left ventricular filling pressure (25.9 ± 1.4 to 22.9 ± 1.2 mm Hg), mean arterial pressure (83.7 ± 5.1 to 77.4 ± 4.1 mm Hg), and systemic vascular resistance (2163 ± 214 to 1528 ± 150 dyne·sec·cm⁻²), all p < .01, without significant changes in heart rate or mean right atrial pressure.

These hemodynamic effects were no longer evident 3 hr after the meal.

Hemodynamic changes 24 to 48 hr after catheterization. To determine whether the postcatheterization and postprandial changes we observed could have been caused by spontaneous diurnal variations and not related to instrumentation or to meals, we performed hemodynamic measurements over a similar period (0900 to 1700 hr) 24 hr later in 12 patients. We observed no significant changes in cardiac index, mean arterial pressure, left ventricular filling pressure, mean right atrial pressure, heart rate, or systemic vascular resistance over a period of 8 hr (table 1). The values for all hemodynamic variables 48 hr after right heart catheterization in these 12 patients were similar to those observed after 24 hr. These 12 patients did not differ from the other nine patients who did not undergo such prolonged observation in the magnitude of postcatheterization hemodynamic changes observed during the initial 24 hr of the study.

There were no significant changes in body weight in any patient during the 48 hr period of observation.

Discussion

Our data indicate that hemodynamic changes that mimic a vasodilator drug response in the absence of drug therapy may occur after right heart catheterization in patients with severe chronic heart failure. Within hours after instrumentation, cardiac index increased and left ventricular filling pressure, mean arterial pressure, mean right atrial pressure, and systemic vascular pressure.

![FIGURE 1. Changes in hemodynamic variables in 21 patients with severe chronic heart failure \(1/2\), 2, 6, and 24 hr after right heart catheterization. Significant hemodynamic improvement was seen in most variables, most markedly with respect to changes in left ventricular filling pressure, over the 24 hr period of observation. Symbols designate significance of difference from \(1/2\) hr values, where * = p < .01 and † = p < .05. All values expressed as mean ± SEM. CI = cardiac index; LVFP = left ventricular filling pressure; MAP = mean arterial pressure; MRAP = mean right atrial pressure; HR = heart rate; SVR = systemic vascular resistance.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.71.4.763)
TABLE 1
Serial hemodynamic measurements performed in 12 patients 24 to 32 hr after right heart catheterization in the absence of medications and mealsa

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
<th>6 hr</th>
<th>8 hr</th>
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<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1.71</td>
<td>1.71</td>
<td>1.70</td>
<td>1.69</td>
<td>1.73</td>
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<td>±0.10</td>
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<td>±0.10</td>
<td>±0.10</td>
<td>±0.09</td>
<td>±0.09</td>
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<td>Left ventricular filling pressure (mm Hg)</td>
<td>26.4</td>
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<td>26.6</td>
<td>26.0</td>
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<td>±2.4</td>
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<td>Mean arterial pressure (mm Hg)</td>
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<td>85.0</td>
<td>85.3</td>
<td>84.3</td>
<td>82.8</td>
<td>81.7</td>
<td>82.4</td>
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<td>±3.7</td>
<td>±3.7</td>
<td>±3.6</td>
<td>±3.6</td>
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<tr>
<td>Mean right atrial pressure (mm Hg)</td>
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<td>12.5</td>
<td>12.5</td>
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<td>11.8</td>
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<td>±2.0</td>
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<td>±1.8</td>
<td>±2.1</td>
<td>±2.3</td>
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<td>Heart rate (beats/min)</td>
<td>81.5</td>
<td>83.3</td>
<td>84.2</td>
<td>85.7</td>
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<td>81.3</td>
<td>82.4</td>
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<td>±2.9</td>
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<tr>
<td>Systemic vascular resistance</td>
<td>1994</td>
<td>2028</td>
<td>2078</td>
<td>2028</td>
<td>1932</td>
<td>1901</td>
<td>1891</td>
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<td>±207</td>
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<td>±174</td>
<td>±168</td>
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</tbody>
</table>

aColumn headings refer to time after initial morning hemodynamic determinations. None of the changes seen at 1 to 8 hr were significantly different from initial values. Data shown as group means ± SEM.

Resistance decreased significantly, and many of these hemodynamic changes were enhanced after patients ate a meal. We observed a further decline in left ventricular filling pressure (without alterations in any other parameter) after patients were permitted to rest overnight, but thereafter the hemodynamic state showed little variability. Hence, hemodynamic improvement may be observed without any therapeutic intervention for up to 24 hr after catheterization and for up to 3 hr after a meal.

The magnitude of the hemodynamic changes that we observed was large enough to mimic a vasodilator drug response. Over the course of 24 hr, excluding postprandial effects, cardiac index increased by an average of 0.23 liter/min/m² and left ventricular filling pressure decreased by an average of 5.9 mm Hg; the magnitude of these responses resembled that seen in patients with heart failure after treatment with isosorbide dinitrate, captopril, and enalapril.16-21 In some patients cardiac index increased as much as 80% and systemic vascular resistance fell as much as 53%; these effects, together with the declines in right and left ventricular filling pressure, resembled the effects of nitroprusside or prazosin.22, 23 Therefore the responses to most vasodilator drugs can be mimicked by the nonpharmacologic changes in hemodynamic variables that were observed in our patients.

We noted these significant shifts in circulatory variables even though we took great care while performing our hemodynamic measurements to ensure physical and emotional stability. All patients were clinically stable under close observation in the hospital before evaluation; all patients were transferred to the coronary care unit at least 12 hr before the study to familiarize them with the new surroundings in an attempt to reduce anxiety. All catheterizations were performed by a single physician, and all of the hemodynamic measurements in an individual patient were performed by the same experienced, highly trained research nurse. The studies were performed in a specially designed bed in the coronary care unit that was shielded from surrounding patients; bed rest was enforced and limited visitors were permitted. Under such controlled circumstances, we have been able to perform measurements with a high degree of reproducibility (less than 10% variation in any hemodynamic variable over a period of 2 hr). We believe that had we not taken such precautions, we would have noted even greater variability in the hemodynamic state.

We suspect that the dissipation of anxiety (apparent or inapparent) caused notable dilatation of the arterial and venous circulations as patients were permitted to rest after right heart catheterization, and this mechanism played an important role in mediating the hemodynamic changes we observed.24, 25 Anxiety-related systemic vasoconstriction may worsen left ventricular performance in patients with congestive heart failure.25 We did not use sedative premedication to reduce emotional stress because of concerns that anxiolytic agents might interfere with the evaluation of the responses to our study drugs; future investigations are needed to determine whether sedatives can effectively attenuate catheterization-induced vasoconstrictor responses or significantly interact with vasodilator or inotropic drugs.

We observed a marked postprandial systemic vasodilator response that caused a notable improvement in cardiac performance in our patients, persisting for
about 2 to 3 hr. Similar beneficial effects on left ventricular function have been previously reported in preliminary communications in patients with coronary artery disease with normal ventricular function as well as in patients with congestive heart failure. The mechanism underlying these effects may be related to the vasodilator and/or inotropic effects of gastrointestinal hormones (glucagon and vasoactive intestinal polypeptide) that are released in response to the ingestion of food. Regional changes in the mesenteric circulation after the absorption of food may also play a contributory role. We have not noted similar responses after the ingestion of small amounts (less than 150 ml) of carbohydrate-containing liquids. The volume and content of food that is necessary to evoke this vasodilator response requires further study.

Although we can easily hypothesize potential physiologic mechanisms that could underlie postcatheterization and postprandial vasodilation, we find it difficult to explain the more gradual but more profound decrease in left ventricular filling pressure that we observed between 2 and 24 hr after intravascular instrumentation. This decline was unaccompanied by significant changes in cardiac index, mean arterial pressure, mean right atrial pressure, or systemic vascular resistance, suggesting that the fall in left ventricular filling pressure was not related to changes in the systemic circulation but could have resulted from alterations in the pressure-volume relationships in the pulmonary circulation and/or in the left ventricle. Of interest, a similar decrease in left ventricular filling pressure without changes in other hemodynamic variables has been observed by Massie et al. in patients with severe heart failure who received placebo 12 to 24 hr after right heart catheterization; these investigators suggested that diurnal changes in the resting hemodynamic state could be responsible for their observations. We could not confirm such diurnal variability, however, when we performed serial hemodynamic measurements 24 to 48 hr after catheterization; hence, the mechanisms underlying this progressive postcatheterization decline in left ventricular filling pressure remain unclear.

Our findings have important implications for the design of hemodynamic studies to evaluate the effects of vasodilator drugs for the treatment of patients with severe congestive heart failure. Previous hemodynamic evaluations have frequently been performed immediately after insertion of the intravascular catheters; after duplicate measurements are made to confirm hemodynamic "stability," the study drug is administered and subsequent hemodynamic changes are assumed to be drug related. During the course of repeated measurements, patients may be moved from the cardiac catheterization laboratory to the coronary care unit, permitted to eat or move from bed to chair, and asked to return to bed for hemodynamic testing at designated times. The personnel performing the hemodynamic determinations may change frequently during the period of observation. After the responses to the first dose are evaluated, the drug may be administered for 24 hr and its effects reassessed before discontinuation of invasive monitoring and initiation of long-term treatment.

The data presented in this article demonstrate that observance of such a protocol may result in a number of erroneous conclusions. Because systemic vasodilator effects may occur after catheterization or after meals, investigators may attribute efficacy to ineffective vasodilator agents or to effective agents administered in subtherapeutic quantities; even if therapeutic doses of active drugs are used, the magnitude and time course of the drug response may be assessed incorrectly. In particular, the postprandial hemodynamic changes mimic closely the onset and dissipation of drug action. Measurements made after 24 hr may appear to show further hemodynamic benefits, especially with respect to changes in left ventricular filling pressure. Similar conclusions may be reached when the drug's effects are reassessed after several months, if hemodynamic measurements made during prolonged treatment are compared with the artifactualy vasoconstricted state observed immediately after the first catheterization; similar degrees of systemic vasoconstriction may not be provoked during the second invasive study. Hence, investigators may report the occurrence of sustained hemodynamic improvement in patients who have not had any real change in left ventricular performance.

In conclusion, in patients with severe chronic heart failure undergoing invasive hemodynamic studies to assess the efficacy of drug therapy, changes in hemodynamic variables may occur after cardiac catheterization and after meals that may mimic a beneficial drug response and invalidate conclusions concerning the effects of short- and long-term treatment. To minimize such responses, we recommend that intravascular catheters be inserted the day before hemodynamic studies and that patients be evaluated in a postprandial state and not be permitted to eat until the hemodynamic measurements planned for that day are completed.

We are indebted to the nurses, fellows, and house staff in the Ames and Rose Coronary Care Units for the excellent care that they provided for our patients.
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Circulation. 1985;71:761-766
doi: 10.1161/01.CIR.71.4.761
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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